A multi-level meta-heuristic algorithm for the optimisation of antibody purification processes

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Abstract

A meta-heuristic optimisation approach using genetic algorithms is presented to aid the design of multi-product biopharmaceutical facilities. Different levels of decision are addressed by the tool and multiple process and business criteria are used to evaluate each alternative. At the purification sequence level, feasible 2-step and 3-step chromatography sequences were generated and evaluated in terms of cost of goods, time and purity metrics. At the unit operation level, a genetic algorithm was developed to determine the best equipment sizing strategy, in terms of column dimensions and number of cycles. The industrial case study provides novel insights that allow the identification of the most cost-effective purification sequences and equipment sizing strategies that meet demand and purity targets for each product in the facility. Graphical plots to visualise trade-offs in the set of optimal solutions are presented so as to enhance the decision making process. For example, the impact of different impurity profiles on the feasibility of the optimal sequences is highlighted using advanced discrete contour plots whilst bubble plots are used to illustrate the impact of different user preferences on the set of optimal equipment sizing strategies.

Keywords: financial business decision-making; process design; bioprocess systems engineering; combinatorial optimisation; genetic algorithms; multi-product facility design; process economics; stochastic decision-support tools.

1. Introduction

Multi-product biopharmaceutical facilities need flexible process configurations that can adapt to products with diverse product and impurity loads so as to avoid bottlenecks and delays, whilst meeting final product specifications and cost targets [1]. This is further complicated by greater batch-to-batch variations owing to the biological nature of biopharmaceuticals in comparison to synthetic chemical drugs. This problem domain poses the challenge of creating optimisation algorithms that can handle multiple levels of decisions simultaneously, combined with several constraints and uncertainties so as to determine how best to design multi-product facilities. In the specific case of monoclonal antibodies (mAbs), a typical purification process uses a set of column chromatography steps and these can represent a significant proportion of the purification material costs, particularly due to the use of expensive affinity matrices as well as the large quantities of buffer reagents required. Interest in switching to newer
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chromatography resins with higher capacities and multiple modes of separation (e.g. high capacity ion exchangers, mixed-mode resins and membrane adsorbers) is considered appealing as the current column approach can continue to be used with the potential of achieving cost or capacity savings [1-3]. In order to address the current challenges, this paper presents a meta-heuristic optimisation approach using genetic algorithms in which multiple decisions, trade-offs and constraints are handled simultaneously so as to determine how best to design multi-product facilities accounting for different optimal purification sequences per product.

2. Methodology

2.1. Overview of the proposed multi-level meta-heuristic procedure

Fig. 1 presents the main steps of the proposed approach with different levels of decision being addressed and multiple process and business criteria are used to evaluate each alternative generated by the tool.

At the facility level, the size of the bioreactor(s) was calculated based on a given ratio of upstream to downstream trains (USP:DSP) and on the demand and titre of each product such that the total number of batches produced in the facility did not exceed the maximum value. At the purification sequence level, a database storing key performance information of a large set of commercial chromatography resins was linked to an enumeration procedure and a detailed process economics model, such that feasible 2-step and 3-step chromatography purification sequences could be generated and evaluated in terms of cost, time and purity metrics. This was repeated for each product in the facility. Then, for each sequence generated, a genetic algorithm (GA) was developed [4] to determine the equipment sizing strategy of each chromatography unit operation, in terms of column dimensions (bed height and diameter) and number of cycles that minimised the cost of goods whilst meeting demand and purity targets. The objective function used to guide the search was the cost of goods per gram (COG/g) [5] which comprised both direct costs based on resource utilisation (e.g. resin costs) and indirect costs (e.g. maintenance costs). The output at this decision level was not one single ‘optimal’ equipment sizing strategy, but a set of alternative strategies with similar values of COG/g. From this set of alternative strategies the average COG/g was
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calculated and used as a performance measure of the corresponding purification sequence. Finally, the overall facility metrics were calculated based on the best sequence per product and on each product’s production share. The multi-level algorithm was built in C# using Visual Studio 2008 (Microsoft Corporation, WA, USA) linked to a database in Microsoft Access (Microsoft Corporation, WA, USA).

2.2. Case study setup

An industrially-relevant case study is presented that addresses the design of a late stage manufacturing facility for the production of 3 mAbs (mAb1, mAb2, mAb3) at different phases of development (mAb1 - Phase III clinical trials, mAb2 and mAb3 - Market), with different titres (3, 4, and 5 g/L), and demands (50, 100 and 350 kg/year). The purification sequence is a 3-step chromatography-based process in which the third step is a membrane chromatography polishing step, common to all products. Table 1 presents the different chromatography resins available for the capture and intermediate purification steps. The specific characteristics of the resins (dynamic binding capacity, unit price) were generated using information from vendors as well as advice sought from industrial experts so as to capture trade-offs in speed, cost and impurity removal capabilities. The range of variation of packed-bed chromatography equipment sizing decision variables was: 15-25 cm bed height, 50-200 cm diameter, 1-10 cycles and one column, in order to address the industry preference for single column processes.

<table>
<thead>
<tr>
<th>Resin</th>
<th>Description</th>
<th>Dbc (g/L)</th>
<th>Price (rmu/L)</th>
<th>LF (cm/h)</th>
<th>Agg RC (max)</th>
<th>HCP LRV Cap</th>
<th>Int</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrA H</td>
<td>Protein A high capacity</td>
<td>50</td>
<td>9200</td>
<td>150</td>
<td>-</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>PrA L</td>
<td>Protein A low capacity</td>
<td>30</td>
<td>6400</td>
<td>300</td>
<td>-</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>PrA gH</td>
<td>Protein A glass high capacity</td>
<td>50</td>
<td>9900</td>
<td>800</td>
<td>-</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>PrA gL</td>
<td>Protein A glass low capacity</td>
<td>30</td>
<td>9000</td>
<td>1000</td>
<td>-</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>CEX H</td>
<td>Cation exchange high capacity</td>
<td>120</td>
<td>2500</td>
<td>500</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>CEX L</td>
<td>Cation exchange low capacity</td>
<td>40</td>
<td>400</td>
<td>300</td>
<td>1-5%***</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CptAd</td>
<td>Capto Adhere (mixed-mode)</td>
<td>150*</td>
<td>3500</td>
<td>375</td>
<td>1-5%</td>
<td>-</td>
<td>1.2</td>
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<tr>
<td>MEP</td>
<td>MEP HyperCel (mixed-mode)</td>
<td>50</td>
<td>1900</td>
<td>100</td>
<td>1-5%</td>
<td>-</td>
<td>1.5</td>
</tr>
<tr>
<td>HA</td>
<td>Hydroxyapatite</td>
<td>35</td>
<td>2700</td>
<td>250</td>
<td>1-5%</td>
<td>-</td>
<td>2</td>
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<tr>
<td>HIC</td>
<td>Hydrophobic interaction</td>
<td>27.5</td>
<td>2500</td>
<td>175</td>
<td>&gt;5%</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Dbc= dynamic binding capacity; r.m.u.= relative monetary units; LF=linear flowrate; Agg RC=aggregates removal capability; (max)= ability to remove agg with this initial level; HCP LRV= host cell protein log reduction value; Cap=capture step; Int=intermediate purification step.

*Load capacity as CptAd runs in flowthrough mode. ** Only if used as intermediate purification or polishing step. If used as capture it does not have any agg removal capability.

3. Results and discussion

Fig. 2a presents a comparison of the different sequences generated by the procedure in terms of % change in COG/g relative to the platform for a fixed chromatography equipment sizing strategy and for a 6USP:1DSP ratio. The platform is a standard process for mAb purification which consists of PrA L for capture, CEX L for intermediate purification and a membrane anion-exchange step for polishing. The fixed
equipment sizing strategy represents a typical industrial practice where the column bed height and number of cycles are set to a fixed value and the diameter is adjusted accordingly. For this case study a 20 cm bed height and 5 cycles are used. The discrete contour plot shows all the possible combinations of capture (y-axis) and intermediate purification steps (x-axis) using the set of available resins described in Table 1. The scenario shown has a very tight DSP window (2 days) so the sequences that offer advantages when the equipment strategy is fixed are the ones with high flowrates (e.g. CEX H - PrA gH). Most of the remaining sequences do not meet demand and the low grams of product result in higher COG/g values (dark grey squares). The use of the GA to optimise chromatography equipment sizing strategies dramatically changes the competitiveness of the sequences as shown in Fig. 2b). Here nearly all sequences offer cost savings when compared to the platform process (medium grey squares), with faster equipment sizing strategies (usually with fewer number of cycles) being used so that more batches can be produced in the planning horizon. The cheapest sequence in terms of COG/g was CEX H – PrA gH. However when impurity removal targets for HCPs and aggregates are considered as well, the set of available optimal strategies becomes reduced as highlighted in Fig. 2b for a product (mAb3) with a very high initial level of HCPs and aggregates. The preferred sequence that is able to meet both HCP and aggregate targets at the lowest cost moves to PrA gH – HA. The tool allowed the improvement of the sequences’ performance by optimising the equipment sizing strategies to account for a tight DSP window, as well as the incorporation of purity targets to choose among alternatives.

Regarding the equipment sizing strategy of each chromatography step in a purification sequence, the GA provides a set of alternative solutions with similar COG/g values. Each bubble plot in Fig. 4 presents a set of strategies generated by the GA with COG/g values that do not differ more than 3% between them, hence allowing for decision-maker’s preferences or facility constraints to be taken into account when selecting the
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strategy to be implemented. If the equipment available in the facility restricts the diameter of columns that can be used (e.g. max diameter = 1m due to space constraints and ease of operation) then solutions that do not meet the requirements can be excluded (black bubbles for mAb3). Due to validation issues there might be the need to tighten the range of variation of the column bed height. The dark grey bubbles strategies would not be feasible if the bed height was required to be limited to between 18 and 22 cm. Finally, if decision-maker wants to minimise the number of columns to purchase, then a 80cm and a 90 cm diameter column would have to be purchased, excluding the strategies represented by light grey bubbles. Therefore the white bubbles are the strategies that meet all criteria.

Fig. 4. Characteristics of the 20 best equipment sizing strategies provided by the GA, for the capture step of the best sequence of each product for a 1USP:DSP ratio. Bubble size is proportional to diameter. Black bubbles: diam>1 m. Dark grey bubbles: bh>22 or <18cm, light grey bubbles: diam ≠0.8m or 0.9m, white bubbles: meet all the constraints.

4. Conclusions
The most cost-effective purification sequences and equipment sizing strategies that meet demand and purity targets were identified for each product in the facility using a multi-level meta-heuristic algorithm. This tool outputs provided novel insights into the design of multi-product biopharmaceutical facilities, particularly in respect to the use of alternative purifications sequences. The decision-making process was enhanced by the use of advanced visualisation tools.

5. Acknowledgements
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References